Normoxic Expression of Hypoxia Inducible Factor-1α Upregulates Iron-Binding Capacity Via Overexpressing Transferrin in Human Hepatoma J5 Cells: A Possible Protective Mechanism for Free Radical-Mediated Insult

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摘要

Abstract

Although living system must have iron to survive, metal-catalyzed generation of various free radicals can cause oxidative stress. Consequently, living systems have evolved strategies to procure adequate iron for cellular function and homeostasis without major damage to biological macromolecules. In this report, we have studied the status of iron homeostasis in five human hepatocellular carcinoma cell lines (HCCs) with varying degrees of differentiation. Among these HCC cells being compared, J5, an intermediate differentiated subline, was found to be notably unique due to its upregulation of total iron binding capacity (TIBC) with value being two- to three-fold greater than other HCC cells compared. By converting this value to transferrin, and iron-binding protein, we noted that J5 also had the highest contents as compared to the rest of HCC cells tested. Conversely, when ferritin, an iron storage protein, was measured, J5 was found to be severely downregulated. To unravel the possible mechanism associated with this observed phenomenon, we then measured the normoxic expression of hypoxia inducible factor 1-~90 兀 (HIF-1~90 兀), a transcription factor known to be a regulator of transferrin and its receptor. Surprisingly, we found that J5 was the only HCC subline capable of expressing HIF-1~90 兀 under normoxic condition. Taken together, we show here for the first time that normoxic expression of HIF-1~90 兀 in a HCC subline may provide a protective mechanism against radical-mediated oxidative damage via upregulating an iron-binding protein (e.g., transferrin) which in turn can alleviate oxidative stress by scavenging metal catalyst (e.g., iron) necessary for the free radical generation (e.g., • OH)